

Experiment Number: C99037B

Route: Gavage, IV

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Test Compound: alpha/beta-Thujone mixture

CAS Number: 76231-76-0

Date Report Requested: 02/07/2017

Time Report Requested: 10:10:25

Lab: Battelle Columbus

Male

Treatment Groups (mg/kg)

	40 ^a	80 ^a	6 IV ^a	40 ^b	
		Brain		Plasma	
C _{0min(pred)} (ng/mL)					
C _{max(pred)} (ng/mL)				185 ± 48	
T _{max(pred)} (minute)				5.32 ± 3.71	
C _{max(obs)} (ng/g) *	976 ± 1080	6180 ± 1450	4030 ± 400		
T _{max(obs)} (minute)	8.67	9.67	5.00		
t _{1/2} (minute)	28.4	88.8	22.8		
t _{1/2(Alpha)} (minute)					
t _{1/2(Beta)} (minute)					
k ₀₁ (minute ⁻¹)				0.522 ± 0.590	
t _{1/2(k01)} (minute)				1.33 ± 1.50	
k ₁₀ (minute ⁻¹)				0.0403 ± 0.023 *	
t _{1/2(k10)} (minute)				17.2 ± 9.8 *	
k ₁₂ (minute ⁻¹)					
k ₂₁ (minute ⁻¹)					
Cl ₁ (mL/min/kg)					
Cl ₂ (mL/min/kg)					
Cl _{1(F)} (mL/min/kg)				7020 ± 2570	
V ₁ (mL/kg)					
V ₂ (mL/kg)					
V _{1(F)} (mL/kg)				174000 ± 71000	
MRT (minute)					
AUC _{0-t}	24800 (ng/g*min)	103000 (ng/g*min)	56200 (ng*min/g)	7660 (ng*min/mL)	
AUC _{inf}	25100 (ng/g*min)	105000 (ng/g*min)	56900 (ng*min/g)	5700 ± 2100 (ng*min/mL)	

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	Treatment Groups (mg/kg)			
	80 ^b		6 IV ^c	
	Plasma			
C _{0min(pred)} (ng/mL)			1160	± 160
C _{max(pred)} (ng/mL)	1060	± 240		
T _{max(pred)} (minute)	7.33	± 4.59		
C _{max(obs)} (ng/g) *				
T _{max(obs)} (minute)				
t _{1/2} (minute)				
t _{1/2(Alpha)} (minute)			4.42	± 0.54
t _{1/2(Beta)} (minute)			20.1	± 3.4
k ₀₁ (minute ⁻¹)	0.448	± 0.413		
t _{1/2(k01)} (minute)	1.55	± 1.43		
k ₁₀ (minute ⁻¹)	0.0194	± 0.0081 *	0.130	± 0.012
t _{1/2(k10)} (minute)	35.8	± 14.9 *	5.34	± 0.51
k ₁₂ (minute ⁻¹)			0.0199	± 0.0059
k ₂₁ (minute ⁻¹)			0.0416	± 0.0086
Cl ₁ (mL/min/kg)			671	± 45
Cl ₂ (mL/min/kg)			103	± 25
Cl _{1(F)} (mL/min/kg)	1270	± 390		
V ₁ (mL/kg)			5170	± 730
V ₂ (mL/kg)			2470	± 410
V _{1(F)} (mL/kg)	65600	± 19900		
MRT (minute)			11.4	± 0.8
AUC _{0-t}	40200 (ng*min/mL)			
AUC _{inf}	63000	± 19000 (ng*min/mL)	8940	± 600 (ng*min/mL)

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	Treatment Groups (mg/kg)			
	40 ^a	80 ^a	6 IV ^a	40 ^b
	Brain			Plasma
C _{0min(pred)} (ng/mL)				
C _{max(pred)} (ng/mL)				204 ± 37
T _{max(pred)} (minute)				6.21 ± 1.89
C _{max(obs)} (ng/g) *	1230 ± 470	4160 ± 1150	3760 ± 920	
T _{max(obs)} (minute)	10	9.33	6.00	
t _{1/2} (minute)	12.9	33	6.39	
t _{1/2(Alpha)} (minute)				
t _{1/2(Beta)} (minute)				
k ₀₁ (minute ⁻¹)				0.237 ± 0.239
t _{1/2(k01)} (minute)				2.92 ± 2.95
k ₁₀ (minute ⁻¹)				0.103 ± 0.079 *
t _{1/2(k10)} (minute)				6.72 ± 5.13 *
k ₁₂ (minute ⁻¹)				
k ₂₁ (minute ⁻¹)				
Cl ₁ (mL/min/kg)				
Cl ₂ (mL/min/kg)				
Cl _{1(F)} (mL/min/kg)				10700 ± 2400
V ₁ (mL/kg)				
V ₂ (mL/kg)				
V _{1(F)} (mL/kg)				103000 ± 73000
MRT (minute)				
AUC _{0-t}	16900 (ng/g*min)	61600 (ng/g*min)	128000 (ng*min/g)	3820 (ng*min/mL)
AUC _{inf}	17000 (ng/g*min)	62500 (ng/g*min)	129000 (ng*min/g)	3750 ± 830 (ng*min/mL)

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	Treatment Groups (mg/kg)			
	80 ^b		6 IV ^c	
	Plasma			
C _{0min(pred)} (ng/mL)			837	± 234
C _{max(pred)} (ng/mL)	683	± 200		
T _{max(pred)} (minute)	6.16	± 4.20		
C _{max(obs)} (ng/g) *				
T _{max(obs)} (minute)				
t _{1/2} (minute)				
t _{1/2(Alpha)} (minute)			4.03	± 0.97
t _{1/2(Beta)} (minute)			26.4	± 29.9
k ₀₁ (minute ⁻¹)	0.407	± 0.483		
t _{1/2(k01)} (minute)	1.7	± 2.02		
k ₁₀ (minute ⁻¹)	0.0433	± 0.0288 *	0.145	± 0.031
t _{1/2(k10)} (minute)	16.0	± 10.6 *	4.78	± 1.02
k ₁₂ (minute ⁻¹)			0.0222	± 0.0086
k ₂₁ (minute ⁻¹)			0.0312	± 0.0363
Cl ₁ (mL/min/kg)			1040	± 140
Cl ₂ (mL/min/kg)			159	± 57
Cl _{1(F)} (mL/min/kg)	3880	± 1550		
V ₁ (mL/kg)			7170	± 2000
V ₂ (mL/kg)			5100	± 6160
V _{1(F)} (mL/kg)	89700	± 44900		
MRT (minute)			11.8	± 7.1
AUC _{0-t}	13400 (ng*min/mL)			
AUC _{inf}	20600	± 8200 (ng*min/mL)	5760	± 780 (ng*min/mL)

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LEGEND

Data are displayed as mean \pm SEM

*Data are displayed as mean \pm SD

MODELING METHOD & BEST FIT MODEL

^a WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Noncompartmental Analysis (NCA).

^b WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; One compartment model with first order absorption and elimination with 1/Yhat weighting (Model No. 3).

^c WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA; Two compartment model with bolus input and first order elimination with 1/Yhat2 weighting (Model No. 8).

ANALYTE

alpha-Thujone

TK PARAMETERS

$C_{0min(pred)}$ = Fitted plasma concentration at time zero (IV only)

C_{max} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max} = Time at which C_{max} predicted or observed occurs

$t_{1/2}$ = λ_z half-life, $t_{1/2}$, the terminal elimination half-life based on non-compartmental analysis

$t_{1/2(alpha)}$ = Half-life for the alpha phase

$t_{1/2(beta)}$ = Half-life for the beta phase

k_{01} = Absorption rate constant, k_a

$t_{1/2(k01)}$ = Half-life of the absorption process to the central compartment

k_{10} = Elimination rate constant from the central compartment also k_e or k_{elim}

$t_{1/2(k10)}$ = Half-life for the elimination process from the central compartment

k_{12} = Distribution rate constant from first to second compartment etc.

k_{21} = Distribution rate constant from second to first compartment etc.

Cl_1 = Clearance of central compartment, Cl_{app} or apparent clearance for intravenous groups

Cl_2 = Clearance of the secondary compartment

$Cl_{1(F)}$ = Apparent clearance of the central compartment, also $Cl_{(F)}$ for gavage groups in non-compartmental model

V_1 = Volume of distribution of the central compartment, includes V_d and V_{volume} of distribution, V_z apparent volume of distribution NCA, V_{app} apparent volume of distribution for intravenous studies

V_2 = Volume of distribution for the peripheral compartment

$V_{1(F)}$ = Apparent volume of distribution for the central compartment includes $V_{d(F)}$, $V_{(F)}$ for oral groups, and $V_{c(F)}$

MRT = Mean residence time

AUC_{0-t} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

AUC_{inf} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

**** END OF REPORT ****